

## BLOOD AND BLOOD SUBSTITUTES

A. DOENICKE, B. GROTE AND W. LORENZ

Each year, in Europe, approximately seven million units of colloidal plasma substitutes are given to patients. Often they are used uncritically, which may account for the increased incidence of side-effects which has been noted over the last decade. Their increasing use is understandable in view of the disadvantages of using blood; these include the difficulties in finding sufficient donors of all the blood groups, the problems of storage of blood and the inherent risks of blood transfusion which include the immunological and toxicological hazards. It should not be forgotten that there are advantages in replacing lost blood with whole blood or blood fractions. These include the similarity of the substitute to the lost fluid, the ability to bind, transport and deliver oxygen to the tissues and the ability to take over the various biochemical functions of the lost body fluids.

### BLOOD

Fortunately, humans normally contain some 25% more haemoglobin than they actually need. The ideal balance between the oxygen transporting capacity of the circulation and the viscosity of the blood is probably better attained when the haematocrit is 30% rather than the more usual 45%.

The primary indication for transfusion is, of course, blood loss. In deciding whether to use blood or plasma substitutes as the replacement fluid, it is necessary to consider the prior condition of the patient. The oxygen carrying capacity of any individual is a function of both the cardiac output and the oxygen concentration of the arterial blood, therefore cardiac reserves need to be taken into consideration. In normal patients a loss of some 20% of the blood volume or a decrease in the haemoglobin concentration to some 9–10 g/dl is well tolerated. The associated volume loss can be managed using plasma substitutes. The limitations to this technique will be seen in patients whose general conditions are poor.

Replacement of intraoperative blood loss with albumin solutions appears to be superior to replace-

ment with dextran solutions (Kallos and Smith, 1974). The total blood loss is less and the need for a transfusion after operation is diminished.

Objective quantitative determinations of blood loss are generally not necessary (Gardiner and Dudley 1962; Underwood, Gowing and Johnston, 1967; Moe, 1970), but because of the particular conditions encountered in infants and small children it is desirable to use either a gravimetric or a photometric method to estimate the actual loss from those patients (Wawersik, 1965).

Blood banks have become almost universally available in the past 30 years. In consequence there is often a thoughtless use of stored blood. After a protest by the Canadian Red Cross in 1973 it was found that 24% of stored blood issued was returned unused and that some 5.5% was lost! The uncritical use of blood is no longer justifiable and with the use of sterile systems with numerous bags it is possible to use the various blood components for specific treatment. The problems related to this have been presented in detail elsewhere (Symposium, 1966).

Blood transfusions may also be needed in anaemic patients. Gillies (1974) has reviewed the problems of anaemia and anaesthesia, which therefore will not be discussed further here.

### *Complications of massive transfusion*

Massive transfusion, that is an exchange of the entire blood volume or more, will necessarily produce complex changes in metabolism and in the coagulation factors. Such complications can be lethal. The diagnostic and therapeutic problems involved have been described in detail by Bunker (1966) and Miller (1973).

Much attention has been given to the survival of the erythrocytes after transfusion, and less to their function. In the past decade the key role of 2:3 diphosphoglyceric acid (2:3 DPG) has been understood (Benesch and Benesch, 1967). Its concentration decreases rapidly in stored blood, thereby shifting the oxyhaemoglobin dissociation curve to the left and impeding the delivery of oxygen from blood to the tissues. Therefore transfusion of red cells will not necessarily mean that there is an improved

transport of oxygen to the tissues. The recovery of normal red cell function requires at least 4 h (Beutler and Wood, 1969) and, after massive transfusion, may take 4–7 days (McConn and Derrick, 1972; Hausdoerfer et al., 1976). The freshest blood available should therefore be used to reduce this problem. In emergency situations this may not be possible.

**Temperature.** The warming of stored blood to body temperature during transfusion has reduced the frequency of ventricular arrhythmias and cardiac arrest (Boyan, 1964). Boyan recommended that warming was necessary only when massive transfusions were given, finding that the oesophageal temperature decreased by only 1 °C after the transfusion of 5 units of cold blood in 90 min. Nevertheless, most workers suggest that all blood transfused should be warmed to minimize the shivering seen after operation which increases the oxygen consumption at a time when cardiac performance may be reduced.

**pH.** Storage of blood in ACD solutions increases its acidity; in addition, metabolism during the storage period progressively reduces the pH. However, following massive transfusion the acid-base state of the patient can fluctuate within wide limits such that a routine administration of sodium bicarbonate is not justified (Miller, Tong and Robbins, 1971). Any correction of the acid-base state should be based on analysis of arterial blood, which may be necessary after the transfusion of each 5 units of blood.

**Citrate intoxication.** The dangers of citrate intoxication have been overrated (Miller, 1973). Only when more than 100 ml/min of blood is transfused will there be a significant but transient decrease in the serum calcium concentration (Denlinger et al., 1976). The prophylactic administration of calcium needs to be considered only in hypothermia or when there is a disturbance of hepato-renal function. Changes in the ECG will probably be the best guide.

**Shock lung.** Many factors need to be considered in elucidating the cause of "shock lung". Certainly one possibility is the obstruction of the pulmonary vascular bed with aggregates from the transfused blood (McNamara et al., 1972). After about 5 days of storage there is a significant increase in the number of aggregates in blood (Harp et al., 1974). Micro-filters will retain these particles (Reul et al., 1973). There are differences between the filters commercially available, and it seems that surface filters are to be preferred (Cullen and Ferrara, 1974; Dunbar,

Price and Canarella, 1974; Buley and Lumley, 1975; Marshall et al., 1976).

**Antibody formation.** Massive transfusion will lead to the formation of iso-antibodies in increasing numbers. The incidence recorded in the literature fluctuates between 1 and 3% (Grobbelaar and Smart, 1967; Maurer and Büttner, 1975; Schricker and Kluge, 1976). Anti-D, anti-Kell and anti-E antibodies were found. With time it is likely that the incidence of finding these antibodies will increase as increasing numbers of patients are given transfusions. Iso-antibodies are frequently found in older patients and in women. They should be sought in any patient who has had a transfusion and who may need another.

**Plasma substitutes and blood typing.** With massive blood loss it will always be necessary for some of the replacement fluid to be blood, even when plasma expanders are used initially. Contrary to earlier reports, the expanders in current use do not produce difficulties in typing or cross-matching, provided that the standard methods are used correctly (Pausch, 1974; Kleine, 1975).

**Transfusion hepatitis.** Hepatitis following transfusion is still an uncontrollable risk. Careful selection of donors and the elimination of those who are Australia antigen positive has not eliminated the risk. The reported incidence of hepatitis following transfusion varies from 0.16 to 6%. In addition, the use of washed red cells has not reduced the risk (Götz, Thoma and Schäfer, 1975). Following the transfusion of more than 4 units of blood, the risk of hepatitis increases by a factor of 2 or 3 (Mosley and Dull, 1966). The production of pooled plasma has largely been abandoned because of the high risk. However, the albumin solutions prepared commercially or by the blood banks are considered safe.

#### *Auto-transfusion*

Three techniques are available to eliminate the risks associated with the transfusion of blood from donors.

**Preoperative removal and storage.** This method, whereby blood is taken from the patient before operation, is limited by the possibility of storing blood for up to only 3 weeks. Experience has shown that it is possible to obtain a number of units of blood from any one patient in this time. Milles, Langston and Dallessandro (1971) began by taking only 500 ml of blood but developed a practice of collecting 3 units, each taken at 2-day intervals, with the last collected 4 days before the operation.

A more complex method which can be applied, especially to patients with rare blood groups, is to take the estimated requirement and preserve the cells by deep freezing. The drawbacks for this method are its limitation to a few centres, its expense and the fact that the thawed cells must be used within 24 h.

*Peroperative collection and haemodilution.* In the past few years plasma substitutes have shown their value in the technique of haemodilution. The principal advantage is that autologous blood is stored beside the patient and can be re-transfused at any time. This can be compared with the disadvantages of transfusing homologous blood. Haemodilution is best carried out by replacing the blood taken with equal parts of albumin and dextran solutions. Under these circumstances there is no increased incidence of bleeding after operation. The advantages and disadvantages of this technique have been discussed in the April 1976 issue of *Anaesthetist*. Whilst a dilution of blood to a haematocrit of 25% is generally tolerated well, it may not be safe in some patients with cardiac complaints.

*Intraoperative autotransfusion.* The autotransfusion of autologous blood has been used during the past century and a half but, with the ready availability of stored blood, has become largely ignored as a technique. It has been used in the United States (Stehling, Zander and Rogers, 1975) and has caught on in many centres in Germany (Feist et al, 1976; Kieninger Junger and Schmidt, 1976; Homann, Klaue and Kult, 1977). The technique may be especially useful in countries in which, for various reasons, the preparation of stored blood is problematical.

There are various circumstances in which autotransfusion is extremely useful, such as the frequent large blood losses associated with vascular surgery and with trauma in the thorax and abdomen, in operations on the liver and in ectopic pregnancies. Contraindications include operations for tumours and for septic abdominal conditions, although the method has been used without complications following trauma to the kidney, bladder and intestines (Kieninger, Junger and Schmidt, 1976). There is a considerable risk of air embolism and any system used must be carefully supervised. Although the plasma haemoglobin concentration increases with this method, there have been no reports of renal failure where a supportive osmotic diuresis has been used at the same time.

The changes produced in blood coagulation by the technique resemble those seen after a homologous

massive transfusion and the experience of those workers cited above shows that the destruction of the coagulation factors by contact with foreign surfaces in the apparatus is slight.

#### PLASMA SUBSTITUTES

The plasma substitutes of greatest clinical use are: the natural colloids (plasma protein solutions, human albumin) and the synthetic colloids (dextran, gelatins and hydroxyethyl starches) prepared from materials derived from animals or plants. Moffitt (1975) has suggested that any synthetic colloid should have the following desirable properties. First, it should maintain an adequate colloid osmotic pressure with a half-life of several hours. Second, it should be stable and capable of being stored for long periods independent of the storage temperature. Third, it should be free of pyrogens and antigens. Finally, its metabolism and elimination should not affect the organism and it should not cause haemolysis or red cell agglutination. The substitutes now available fulfil some of these conditions, but other effects have appeared which have led to a flood of partially contradictory publications in the past few years. The following are the most important, commonly used, commercially available plasma substitutes:

*Dextran.* Dextran is produced by the bacterium *Leuconostoc mesenteroides* B512 from an agar-sugar compound to which a yeast extract is added as a source of nitrogen. In preparing dextran solutions the degree of variation in the polysaccharide chains is important as well as the average molecular weight. Dextran 40 has a mean molecular weight of 40 000 and Dextran 60 and 70 molecular weights of 60 000 and 70 000, respectively.

*Gelatin.* Gelatins are prepared by the hydrolysis of animal collagens (bones, etc.). There are three modified solutions available: a modified fluid gelatin, a urea-linked gelatin and an oxypoly gelatin.

*Starch.* Starch solutions prepared by the acid hydrolysis of corn or soya may be used as plasma expanders only after the introduction of hydroxyethyl groups into the glucose units. To obtain a satisfactory half-life in the circulation the commercially available solutions have hydroxyethyl units attached to 70% of the glucose units.

#### Indications for use of plasma substitutes

The principal indication for the use of colloid plasma substitutes is in the treatment of hypovolaemia. They have shown their value in the treatment of shock following accidents. There are

TABLE I. *Production and properties of different colloidal plasma substitutes*

| Substitute     | Production   | Types   | Mean molec. wt.  | Intravascular half-life | Indications   |
|----------------|--|---|------------------|-------------------------|---|
| Plasma protein | Human plasma, placenta   | Serum conserves<br>Human albumin<br>(5% and 20%)  | 50 000           | 4-15 days               | Volume substitution,<br>hypoproteinaemia,<br>haemodilution  |
| Dextran        | B. <i>Leuconostoc mesenteroids</i> B512 on agar-sucrose plates | D 60/75<br>D 40                                   | 60 000<br>40 000 | 6 h<br>2-3 h            | Haemodilution<br>Microcirculation disturbances<br>(Both:) Volume substitution, thrombosis prophylaxis |
| Gelatin        | Hydrolysis from animal collagens                               | Modified gelatin<br>Urea-linked<br>Oxypolygelatin | 35 000           | 2-3 h                   | Volume substitution   |
| Starch         | Acid hydrolysis and ethylene oxide treatment of soya and corn  | Hydroxyethylene starch                            | 450 000          | 6 h                     | Volume substitution,<br>haemodilution   |

large differences between the various solutions in terms of the changes they produce in blood volume and in the duration of their effects (table I). For example, the duration of action of Dextran 60 is about 6 h as is that of hydroxyethyl starch (HES), whilst gelatins and Dextran 40 last only 2-3 h.

The increase in blood volume is least with gelatin. Strey and his colleagues (1977) have studied the effects of plasma substitutes and noted initially that 90 min after the removal of 1 litre of blood the reduction in the measured plasma volume was only 200 ml. Therefore 400 ml or so of fluid must have entered the plasma from the extravascular spaces in that period. The infusion of 1 litre of Dextran 60 led to small increases in plasma volume and blood volume above the initial values. It took 4 h for the blood volume to be restored to the initial control value. Strey and colleagues (1977) also measured the duration of the effect of dextran. About 56% of the infused dextran was still in the blood 4 h after termination of the infusion. This represents 34 g of dextran which would hold 700 ml of water. In addition, they showed that this infusion produced a decrease in the peripheral systemic resistance with an increase in venous return and cardiac output. These effects must be beneficial for tissue perfusion and were detectable especially in the renal effects.

In this context it is interesting to compare the serum concentrations of Dextran 60 and HES found by Boon and colleagues (1976) in a study in volunteers. The elimination of HES from the blood followed a

protracted course. Two weeks after the infusion the HES concentration was still 9% of the initial value and at 17 weeks was still greater than 1%. In contrast, Dextran 60 was undetectable 4 weeks after its infusion.

In addition to the use in hypovolaemia there are some additional indications for using plasma protein solutions and dextrans. Plasma protein solutions can be used where there is hypoproteinaemia or where plasma clotting factors are deficient. The two other features of dextrans are their antithrombotic effect and, especially with Dextran 40, the effect of improving the microcirculation.

Gruber and his colleagues (1975) have shown in 28 randomized controlled studies, that the incidence of thromboembolic venous thrombosis was 35% in patients undergoing general surgery, but that when dextrans were given during or after operation the incidence was reduced significantly.

The improvement of the microcirculation by the infusion of hyperoncotic Dextran 40 is of use in the treatment of peripheral and cerebral perfusion disturbances (Herrschaft, 1975; Gottstein, Sedlmeyer and Heuss, 1976).

#### *Reactions to plasma substitutes*

There are incompatibility reactions to plasma substitutes; they are diverse in nature and need to be studied in detail. The reported incidence of such reactions varies between 2.0% (Rudowski et al., 1973) and 19% (Schöning and Koch, 1975). The

increased *reported* incidence of reactions leads us to assume that there is an *actual* increase. In order to examine this problem, Ring and Messmer (1977) performed a controlled prospective comparative study in 31 hospitals in Southern Bavaria. They observed 69 anaphylactoid reactions following 100 906 units of the commonly used colloidal plasma substitutes. There were differences between the agents: following plasma proteins there were reactions in 0.014% of patients, following dextran in 0.032%, following gelatins in 0.115% and following hydroxyethyl starch in 0.085%.

The types of anaphylactoid reaction seen varied in intensity from skin reactions with flushing and mild urticaria to more severe effects such as shock and cardiac and respiratory arrest (Lorenz et al., 1976). Ring and Messmer (1976) divided such reactions into four types (table II). The frequencies of life-endangering reactions were: 0.003% for

TABLE II. *Severity scale for quantification of intensity of anaphylactoid reaction*

| Grade | Symptoms   |
|-------|--|
| I     | Skin symptoms or mild fever reaction, or both  |
| II    | Measurable, but not life-threatening<br>Cardiovascular reaction (tachycardia, hypotension)<br>Gastrointestinal disturbance (nausea)<br>Respiratory disturbance |
| III   | Shock, life-threatening <i>spasm</i> of smooth muscles (bronchi, uterus, etc.)   |
| IV    | Cardiac or respiratory arrest, or both   |

plasma proteins, 0.008% for dextran, 0.038% for gelatins and 0.001% for hydroxyethyl starch. These data and our personal observations (Lorenz et al., 1971, 1976; Doenicke, 1976) lead us to conclude that no colloid substitute can be given without risk.

Lorenz and his colleagues (1977) have determined the extent to which histamine release is involved in these reactions and investigated whether it is the predominant mediator. A randomized controlled trial was carried out in humans and dogs. The humans received either Dextran 60, gelatin cross-linked by hexamethylene diisocyanate (Haemaccel), oxypolygelatin (Gelifundol) or high molecular weight hydroxyethyl starch (Plasmasteril). The dogs were given either dextran 60, Haemaccel, Gelifundol, Plasmasteril, gelatin cross-linked by succinic acid anhydride (Neoplasmagel) and phosphatidyl serine (PS), dextran 60 and PS or Plasmasteril and PS. In the humans plasma histamine concentrations (Lorenz

et al., 1972) were measured together with the heart rate and arterial pressure and in the dogs the whole blood histamine concentrations (Lorenz et al., 1974) and the arterial pressures were measured together with investigations into the macroscopical and microscopical pathology. In man all four plasma substitutes released small, clinically unimportant, amounts of histamine. This was unrelated to the occurrence of urticaria except with Haemaccel. One girl developed a generalized urticaria following the oxypolygelatin infusion, but this was not associated with any increase in plasma histamine.

Similar results were obtained in the dogs. When Haemaccel produced hypotension this was accompanied by a correspondingly large increase in whole blood histamine. Severe hypotension occurred less frequently with the other substitutes and was not accompanied by the release of histamine. Phosphatidyl serine did not release histamine in dogs, but there was a greater release when it was combined with dextran or hydroxyethyl starch than when these expanders were used alone.

The skin reactions with the plasma substitutes in man did not show any relation to the histamine concentrations. This might be a result of either the reactions not being caused by histamine release, or the release in the skin being small and insufficient to show systemic effects and increased plasma concentrations, although adequate for the skin reaction.

It was concluded that histamine can be released in humans by gelatin (Haemaccel) and to a smaller degree by dextran. When accidents occurred in clinical practice histamine was found in every case when Haemaccel was used. In two severe incidents with dextran (one fatal) no significant increase in the plasma histamine concentration was found.

It seems, therefore, that reactions to Haemaccel are related to the release of histamine and are probably the result of a direct effect of the drug on mast cells. This may be clinically important with the development of further specific  $H_1$  and  $H_2$  receptor antagonists which may give better control of such reactions. Ring and Messmer (1977) believe that the severe anaphylactoid reactions to dextran are probably related to antidextran antibodies such as IgG and IgM which have been found in high concentrations in all patients with severe reactions. The recorded reactions after hydroxyethyl starches may not be caused by histamine release, but may involve kinins. With their close similarity to starch, an anaphylactoid reaction mediated by humoral mechanisms might be the cause (Doenicke, 1976).

TABLE III. *Pathological mechanism of anaphylactoid reactions after colloidal infusion (Ring and Messmer, 1977)*

| Colloid        | Reaction types     | Mechanism                             | Authors                        |
|----------------|--------------------|---------------------------------------|--------------------------------|
| Plasma protein | Immediate reaction | Protein allergy, aggregates           | Ring and others (1974)         |
|                | Late reaction      | Aggregates, stabilizers               | Ring (1976)                    |
| Dextran        | Mild reaction      | Allergic disposition                  | Ring (1976)                    |
|                | Severe reaction    | Anti-Dextran antibodies (IgG and IgM) | Ring and Messmer (1977)        |
|                |                    | Complement activation                 | Johnson and Laurell (1974)     |
| Gelatin        | Immediate reaction | Histamine release                     | Lorenz and others (1971, 1976) |
|                |                    |                                       | Doenicke and Lorenz (1977)     |
| Starch         | Immediate reaction | Complement activation                 | Ring and others (1976)         |

The term "anaphylactoid reaction" should be understood in this context as any undesirable hypersensitivity as shown by the classical anaphylactic reactions. The reactions are individually specific and independent of the mechanisms of action of the drugs. Table III summarizes the reaction and mechanisms for the differing plasma substitutes.

In anaesthetic practice Bauer and Östling's (1970) observation, that most reactions occur immediately after the infusion of only a few millilitre of the substitute, is important. Detailed observation is thus necessary in this stage of treatment if major problems are to be avoided.

In treating reactions we use the same rules as for those seen with other anaesthetic drugs (Doenicke and Lorenz, 1970). They seem to be equally effective for plasma substitutes. If there is only mild urticaria, stopping the infusion usually is all that is needed, but if the urticaria is severe, calcium antihistamines and corticosteroids should be used. In acute problems with circulatory failure adrenaline 0.05–0.1 mg should be given immediately with further injections at 1–2 min intervals as required. High doses of corticosteroids should also be given and the plasma volume should be expanded using a human albumin solution.

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